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E D I T O R I A L

TECHNICAL PROGRESS AND GENETIC RETROGRESSION

ON OUR cover this month, we picture the co-discoverers of the new adrenocorticosteroid, "Decadron", which chemically is 16α-methyl-9α-fluoroprednisolone. This, the most recent of the synthetic glucocorticosteroids, is even more potent than prednisolone which, in turn, is more potent than the naturally produced hydrocortisone. Other potentiated steroids are also known and great credit is due those painstaking workers who have succeeded, after only a few years, in improving on nature's own products, developed after many millennia of evolutionary change.

To say that any new chemical, foreign to the human body, will perform in all respects better than a natural biochemical substance is extremely optimistic for only time and experience can give a positive answer to this question. It is, however, a tribute to modern pharmaceutical technology that new compounds with such amazing properties can be tailor-made in the laboratory.

It is progress such as this as well as in the many other areas of public health which has raised life-expectancy to the biblical three score years and ten and promises still more as the process of aging and the degenerative diseases are given greater attention.

As with all human achievements, however, this is not all to the good and for the betterment of mankind. Gradually, it is dawning on those who look beyond the immediate present and the near future that we may slowly but surely be setting the stage for man's retrogression and eventual disappearance from the earth as, today, we know him. The ironic thing is that the factor which may lead to this catastrophe is that very progress which we have made and are making in the prevention and cure of disease. While it is a very humane and proper thing to save lives and save the weak, the extension of this process to the point that it becomes the almost universal practice may ultimately destroy the species. The laws of nature are quite inexorable and they can no more be altered than can one's

genes which, in the final analysis, determine what we are or, at least, what we are likely to be. Of course, we can alter genes by mutation but this rarely produces an improvement in the species and almost always can be expected to do harm.

Through the process of natural selection down through the ages, man has become the superior and superlative creature which he now is. Down through this long period of time, the weak and the unfit failed to survive and, thus, failed to procreate other weaklings and inferiors such as themselves. While it is, of course, tragic for any child to succumb, it is even more tragic as far as the species is concerned for the genetically unsound and unfit to pass their genes on to others and future generations.

By the appropriate use of today's miracle drugs, thousands upon thousands of those who are inferior genetically manage to survive and have offspring. This coupled with the ever increasing genetic damage which is done by radiation, both cosmic and man-made, adds still more murk to the already murky waters of human destiny. To add still further to human woes is the philosophy that it is every person's privilege, even if he be a moron, to have as many offspring as he wishes and thereby to pass on to them those inherent weaknesses which cannot be altered or corrected by any known means.

The ironic thing about the whole situation is that the more highly advanced the nation's civilization and technology, the more likely it is that natural selection will not weed out those whose contribution to the genetic pool is harmful.

While one who propounds such philosophy is not likely to be popular and runs the risk of ridicule, the fact remains that this is a human risk as great as that posed by the atomic bomb. Already, we have evidences in this country that some of these negative factors are at work, and one does not have to look too closely in order to find them. The answer, of course, is not to do away with our modern drugs and all technical progress. It would seeem to lie more in correcting our critical need for improving the social consciousness of our people, their personal sense of responsibility to one another, to future generations and to their Creator.

L. F. Tice.

THE SYNTHESIS AND STUDY OF QUINIDINE POLYGALACTURONATE * [a]

By Alfred Halpern,** Norman Shaftel †
and A. J. Monte Bovi ‡

A RECENT study (1) of the problems associated with the toxicity of quinidine therapy suggested the need for an agent with a lower index of gastrointestinal distress. This report describes the synthesis and study of a new complex glycosidic quinidine salt which has been determined (2) to be a valuable therapeutic agent and which is not limited by the alimentary tract complications so frequently associated with the use of the conventional alkaloidal salts (1, 3).

While gastrointestinal distress after quinidine therapy may be due to either a central nervous system toxicity or a local alimentary tract irritation, it is the consensus of opinion (1, 3, 4) that this adverse symptomatology most often arises because of local irritation. To enhance the well known and therapeutically desirable pharmacologic and clinical behavior of quinidine, our efforts were directed toward a means of modifying this local toxic response of the conventional salts of quinidine without altering its essential pharmacology or its therapeutic cardiac effects.

The inorganic acid salts are the most commonly prescribed quinidine compounds, and, because of their polar character, are strongly dissociated in physiologic fluids. The possibility that the local gastrointestinal irritation results from the flood of both basic and acid ions was considered, since the presence of materials (5, 6) which tend to depress this ionization in the gastrointestinal tract, pro-

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* From the Department of Experimental Therapy, The Stuyvesant Polyclinic, New York City. [a] Quinidine polygalacturonate is available as Cardioquin[t.m.] from the G. F. Harvey Company, Saratoga Springs, New York.

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vides some degree of palliative relief. The fact that a reduction in dosage of the drug has been shown (7) to affect the incidence of alimentary distress further points to a threshold limit of ionic concentration for such occurrence.

In order to avoid this local ionic tissue shock, the synthesis of a weakly ionizable quinidine compound, which would make available to the heart the active quinidine moiety at a uniform rate, was planned. It was postulated that such a molecule should be only slightly soluble in physiologic fluids since, according to the law of mass action, the number of ions present in a system at any given time is a function of the quantity of the compound in solution, as well as its degree of dissociation. The dynamic character of physiologic absorption should provide a uniform supply of the compound by removing the dissolved components from the system, thereby bringing additional material into solution.

To produce a slightly soluble as well as a weakly dissociable compound, polygalacturonic acid was selected as the acidic component of this molecule. This long chain carbohydrate polymer is not absorbed (8) across the gastrointestinal mucosa and consequently would remain in the alimentary tract to provide a continuous buffer action to basic ions as well as contributing a mucin-sparing colloidal demulcent effect (9, 10).

The polygalacturonic acid moiety, which is derived from pectin, has already been noted to possess special protective properties for the gastrointestinal tract (11-17), and the versatility of polygalacturonic acid in allaying local intestinal mucosal irritation arising from widely varied etiologies has been reported (11, 12, 13). The polygalacturonates were shown to produce improvement in the symptoms of abdominal distress, distention, nausea and anorexia associated with enterocolitis (14) and the use of this agent to allay the diarrheas of bacillary dysentery was described by Tompkins (15). The detoxifying properties of the polygalacturonates were noted by Winters et al. (16) who described the protective properties of this material against peptic ulcer induction by cincophen. Manville and associates (17) studied the detoxification of lead and arsenic by polygalacturonates and reported striking protective effects.

Quinidine alkaloid is a basic compound (K value of 2.2×10^{-7}), capable of forming monobasic and dibasic salts with both inorganic and organic acids. While numerous quinidine derivatives have been

prepared (18, 19, 20) these compounds were largely the simpler inorganic and organic salts.

Polygalacturonic acid is a long chain carbohydrate containing between 50 and 400 galacturonic acid units in typical 1,4-glycosidic linkage. Each available carboxyl group is capable of reacting with a quinidine molecule to form a polymeric salt, quinidine galacturonate in systematic, geometric spacial orientation.

Experimental

Quinidine polygalacturonate was prepared through a modification of the method described by Stuewer and Olsen (21) for quinine pectate. From the experiences of these workers, it was indicated that an insoluble compound permitting easy separation, would result. However, preliminary trials indicated that quinidine polygalacturonate, in contrast to quinine pectate, remained soluble in the aqueous alcoholic medium and that vacuum distillation of the solvents would be necessary to isolate the compound.

The general synthetic procedure adopted was to react stoichiometric equivalents of quinidine alkaloid and polygalacturonic acid in an hydroalcoholic medium. The course of the reaction was followed by determining the shift in the pH of the medium. When the reaction had progressed to completion, the solvents were evaporated under reduced pressure and the product isolated. Purification was achieved through recrystallization from alcohol or by selective solvent extraction. The compound was obtained as a creamy white solid, containing one molecule of water of hydration, and the structural formula may be postulated as represented in Figure 1.

The neutralization equivalent of a sample of the polygalacturonic acid was determined by titration with N/10 sodium hydroxide solution. The stoichiometric equivalent of the polygalacturonic acid (based upon the quantity of quinidine alkaloid used) was suspended in distilled water and heated to 75° C., under constant stirring. (A weight/volume ratio of 1:40 between the acid and the water was found to be preferable.) To this suspension was slowly added a ten per cent solution of quinidine base in methanol which had been previously heated to 60°-70° C. The stirring and heating (at 70° C.) were continued until complete solution was achieved. The pH of the solution was determined and the reaction continued until successive

pH determinations indicated no further changes. The solution was then allowed to cool to room temperature and the solvents distilled under reduced pressure until a thick slurry of precipitate solids resulted. The slurry was filtered and the solids washed twice with small portions of methanol followed by ether and dried in a vacuum oven at 40° C., until no further loss in weight occurred. The yield of quinidine polygalacturonate was better than 90 per cent of theory.

Quinidine polygalacturonate was obtained as a creamy, white amorphous powder, melting at 180° C. with decomposition. It analyzed for $(C_{26}H_{34}O_9N_2 \cdot H_2O)_x$: with x equivalent to values of from 50 to 200 dependent upon the particular chain length of the polymer utilized. (Carbon: theory, 58.18; found, 58.03; Hydrogen: theory, 6.76; found, 6.52; Nitrogen: theory, 5.22; found, 5.04). The

QUINIDINE POLYGALACTURONATE

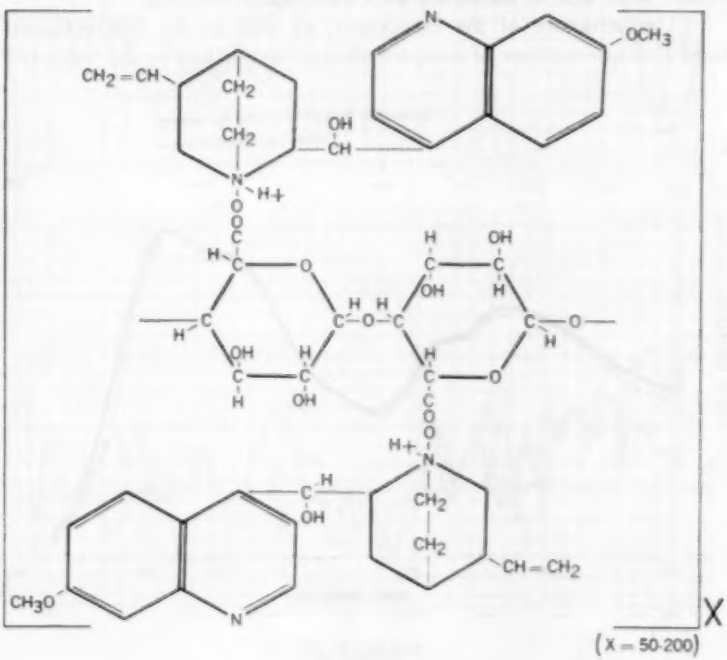

FIGURE 1

compound assays for 60.46 per cent of quinidine, on an anhydrous basis.

The dried product is virtually insoluble in organic solvents (methanol, ethanol, chloroform, ether, acetone and dioxane). It is soluble (12 per cent) in hot, 40 per cent methanol or ethanol solutions and to the extent of approximately two per cent in water at 25° C. Continuous extraction with organic solvents failed to separate the components of the compound and analysis of the aqueous soluble fraction indicates that it has the same quinidine ratio as the starting product.

As would be expected, the formation of a glycosidic salt of the alkaloidal base did not exert an appreciable effect on the general character of the ultra-violet absorbancy curve. The curves (Fig. 2), plotted as ratios of E/E_{max} over the pertinent spectral region for solutions of the compound and quinidine base in both 0.1N hydrochloric acid and in methanol were essentially identical.

The structure of the compound, as well as its differentiation from a simple mixture of components was established by the infra-red

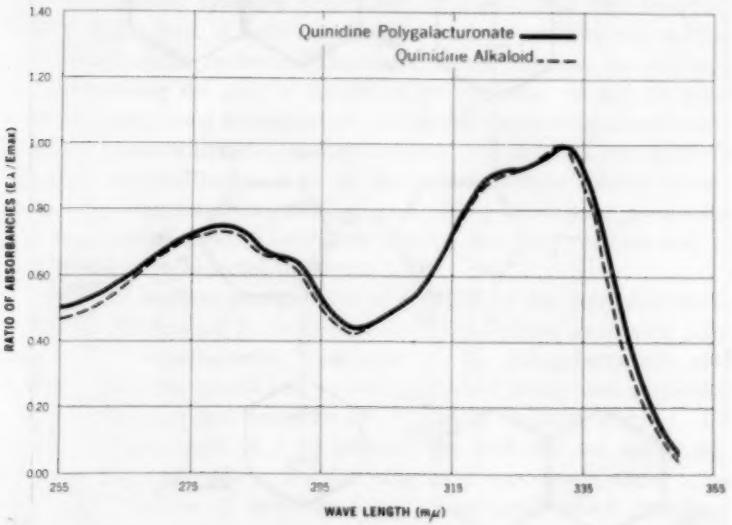

FIGURE 2

The comparative ultra-violet spectrum of quinidine polygalacturonate and quinidine alkaloid in methanol.

spectra. Infra-red spectral analysis was conducted with both the isolated compound quinidine polygalacturonate, and an intimate mixture prepared by grinding stoichiometric equivalents of quinidine and polygalacturonic acid. The readily apparent differences between the two curves (Fig. 3) confirms the formation of a true compound.

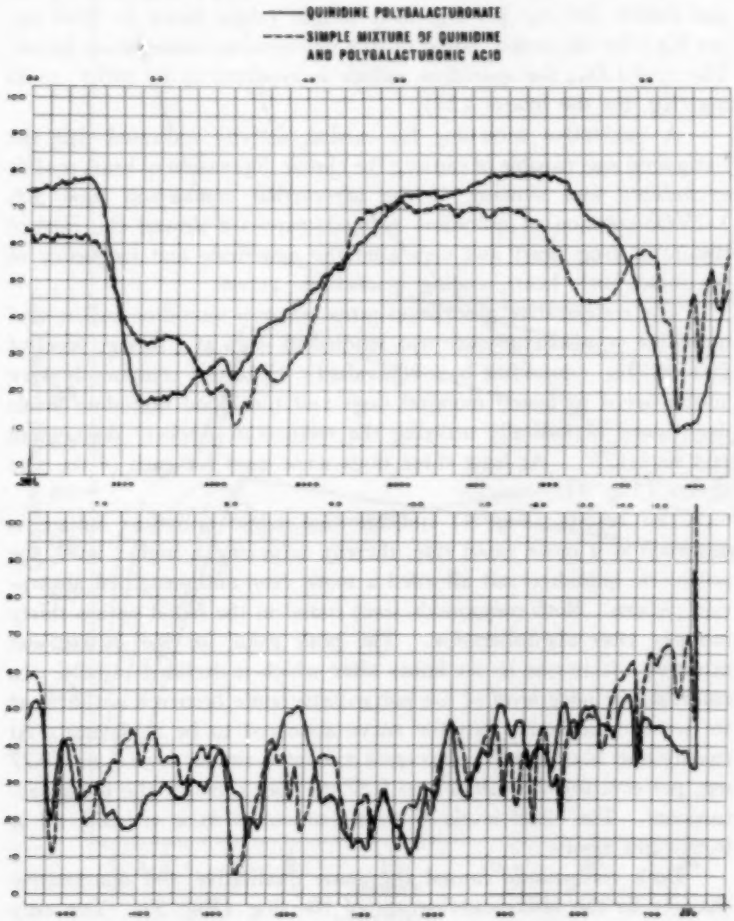

FIGURE 3

The comparative infra-red spectrum of quinidine polygalacturonate and a simple stoichiometric equivalent mixture of quinidine and polygalacturonic acid.

Pharmacology

The acute oral toxicity of quinidine polygalacturonate was studied (22) in rats and mice. The method of Miller and Tainter (23) was used to compute the LD_{50} and this was found to be 3200 ± 350 mg. per Kg. body weight (slope factor = 3100 mg. per Kg.) for the rat and 2680± 210 mg. per Kg. body weight (slope factor = 1840 mg. per Kg.) for the mouse, based upon a fourteen-day observation period. The oral LD_{50} for quinidine sulfate is reported to be 593.1 ± 83 mg./Kg. for the mouse (24).

A qualitative screening for cardiac activity indicated that the compound was capable of causing the classic depression of heart muscle excitability and slowing of the myocardial conduction time. A 1:25000 solution of quinidine polygalacturonate slowed the rate of the intact frog heart and decreased the amplitude and frequency of the intact turle heart, ending in diastolic arrest.

The comparative absorption rates between quinidine sulfate and quinidine polygalacturonate was studied in dogs at a dosage level of 100 mg./Kg. (quinidine base equivalent). The test compounds were administered to fasted mongrel dogs and the blood quinidine levels determined periodically utilizing the method of Archer, Weitzmann and Kay (25). At least three dogs were used for each of the test agents (Fig. 4).

The results (Fig. 4) indicate that while quinidine sulfate is absorbed at a more rapid rate, thereby achieving a higher level, the polymeric quinidine salt afforded a more even and sustained absorption pattern. Both compounds were found in the blood within thirty minutes after administration. The peak value for the sulfate was achieved within one to six hours after which it declined rapidly. In contrast, the peak level of the polygalacturonate occurred within four to twenty-four hours, but the curve appeared to be a plateau. At twenty-four hours, both compounds exhibited similar levels, with 0.77 mg. per cent for the sulfate and 0.87 mg. per cent for the polygalacturonate. The blood levels of both compounds were virtually nil at forty-eight hours.

Both compounds caused the same qualitative and quantitative changes in the electrocardiogram of the dog (Fig. 5). The only noticeable variation was the time of onset of these changes which was observed earlier with the sulfate due to its more rapid absorption.

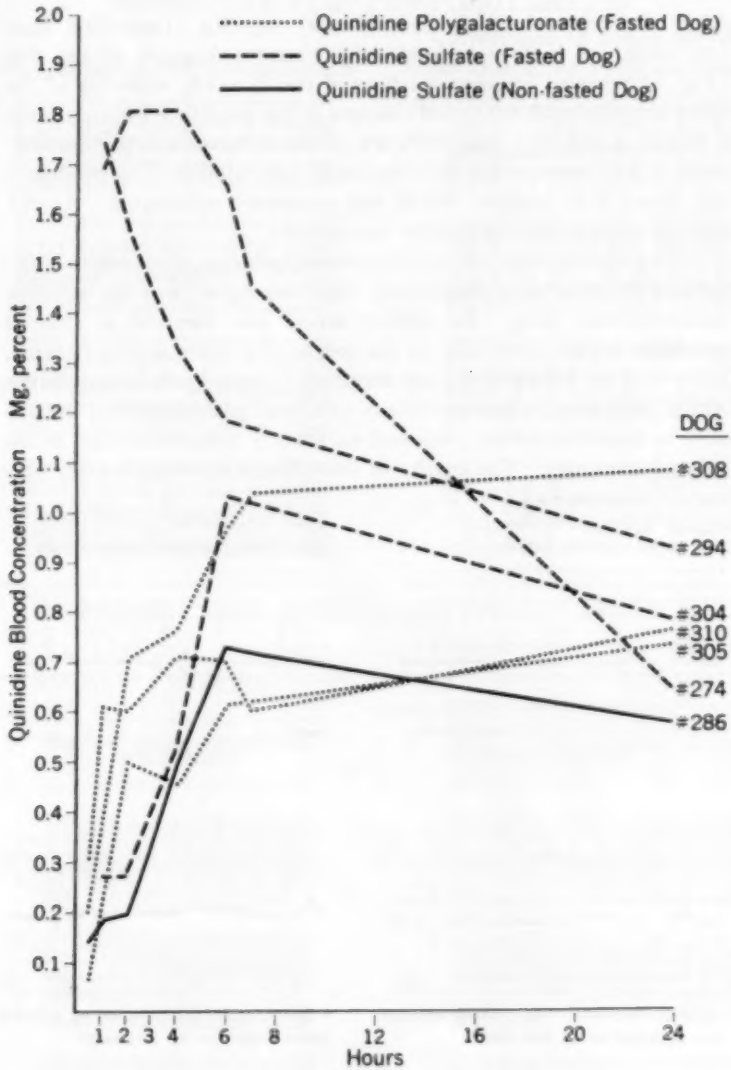

FIGURE 4

A comparison of the quinidine blood levels observed after the administration of equivalent doses (100 mg. quinidine base/Kg.) of quinidine sulfate and quinidine polygalacturonate to dogs.

After the relatively high dose of 100 mg./Kg. (quinidine base equivalent) of both compounds, the electrocardiogram of the dog (Fig. 5) revealed frequent notching of the P waves, widening of the QRS complex with reciprocal changes in the amplitude between leads I and II, a notching near the apex of the R wave, and the development of a U wave which later coalesced with a taller T to produce a tall, broad T-U complex which was commonly unbilicated. An ST depression was less frequently encountered.

The investigation (2) of the clinical behavior of quinidine polygalacturonate in man established that this agent was an effective antiarrhythmic drug. Its cardiac action was identical to that of quinidine sulfate (Fig. 6). In the course of a study of fifty patients, there were no instances of gastrointestinal distress encountered. Some of the patients who had previously exhibited gastrointestinal intolerance to quinidine sulfate presented no adverse symptomatology to the polygalacturonate. The results of this clinical investigation are presented elsewhere (2).

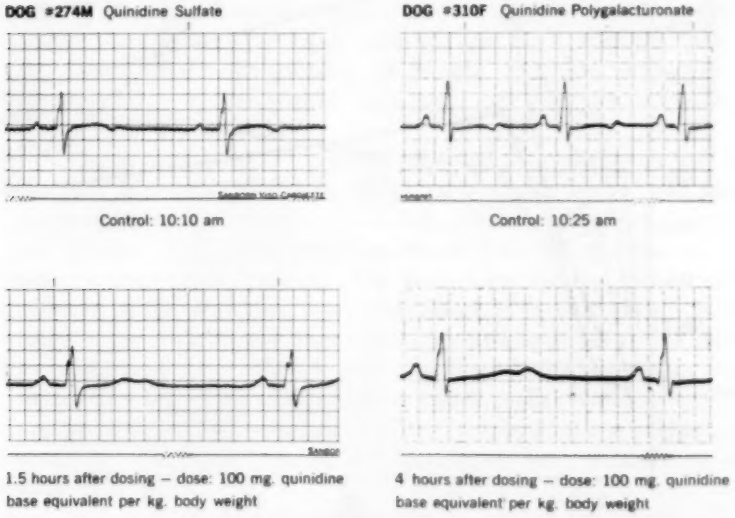
DOG #274M Quinidine Sulfate
DOG #310F Quinidine Polygalacturonate
Control: 10:10 am
Control: 10:25 am
1.5 hours after dosing – dose: 100 mg. quinidine base equivalent per kg. body weight
4 hours after dosing – dose: 100 mg. quinidine base equivalent per kg. body weight

FIGURE 5

The effect of quinidine sulfate and quinidine polygalacturonate on the ECG of the normal dog.

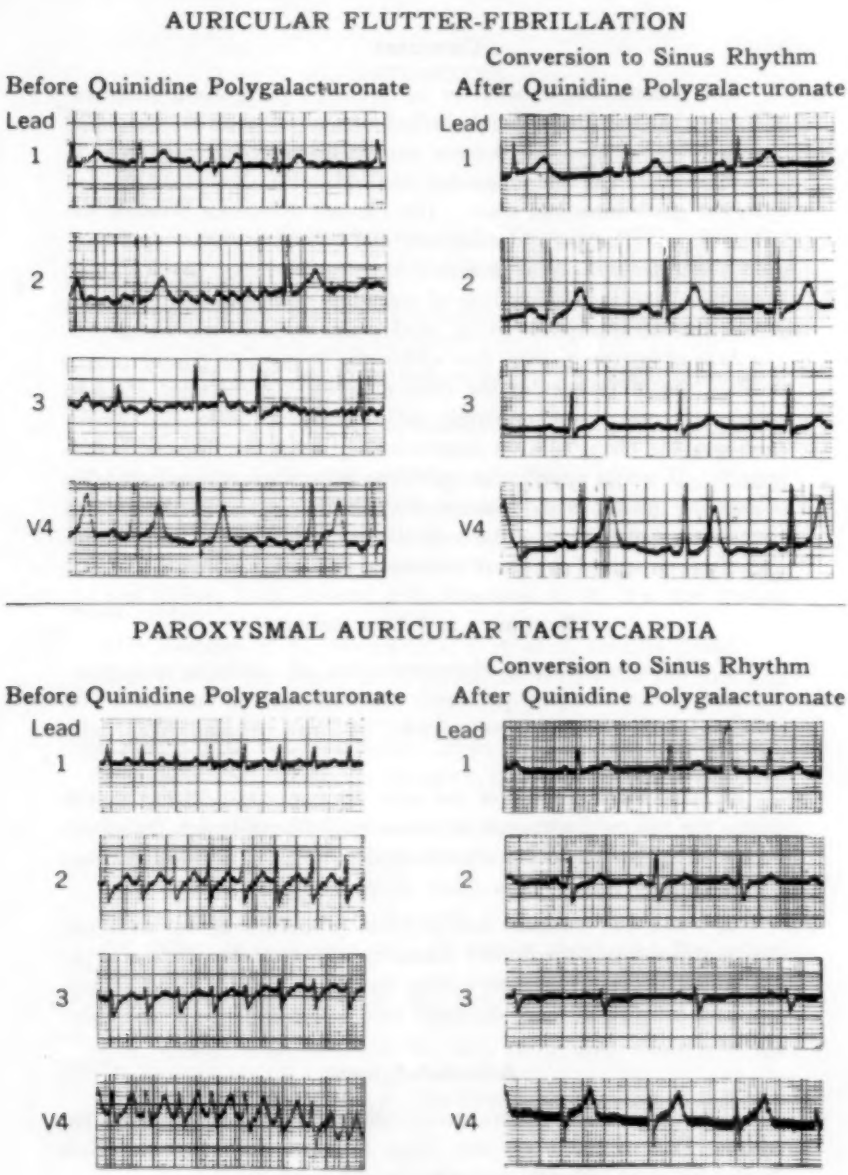

FIGURE 6

The antiarrhythmic effect of quinidine polygalacturonate in a patient with auricular flutter-fibrillation, and a patient with paroxysmal tachycardia.

Comment

The pharmacologic behavior of quinidine polygalacturonate established that the fundamental cardiodynamic properties of quinidine have not been altered. The more sustained absorption pattern is in part, a reflection of the controlled availability of the quinidine ions from the gastrointestinal tract. The marked difference between the LD_{50} of quinidine polygalacturonate and quinidine sulfate also suggests a modification of the amount of the drug absorbed per unit time. Because of the rapid excretion of quinidine from the body (26), a slower rate of absorption would modify the value of the LD_{50}.

It is of interest to note that within the therapeutic dosage ranges in man, the differences in the rates of absorption between the two compounds were not apparent (2), and the onset of electrocardiographic changes were approximately the same for both compounds. It would appear that quinidine polygalacturonate is capable of exerting the full cardiodynamic effects of the conventional quinidine compounds, but because of the controlled availability of quinidine ions, the effects produced are more uniform.

Summary and Conclusions

1. The synthesis and characterization of quinidine polygalacturonate, a new complex polymeric alkaloidal salt is described. Its structure and identity are confirmed by infra-red and ultra-violet spectral analysis.

2. The pharmacology of the new compound establishes that it exerts the full cardiodynamic action of quinidine although the effects produced appear to be more uniform than those of the conventional inorganic salts.

3. From the chemical and physical properties of the molecule, it is postulated that the limited solubility and weak dissociation of the compound are principal contributing factors to the controlled absorption and consequent more desirable cardiac activity.

Acknowledgment

The authors are grateful to Dr. Kenneth Morgareidge and Dr. Myron Brin of the Food and Drug Research Laboratories (New York) for their technical assistance in this study.

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LIMITATIONS IN THE CHEMICAL TREATMENT OF ACUTE LEUKEMIA

A Summary of 7576 Cases

By John R. Sampey *

THE acute leukemias are not as responsive to chemotherapy as the chronic forms of myelocytic and lymphocytic leukemia.[1] In 1950 F. W. Gunz of the University of Cambridge wrote: "The treatment of acute leukemia is distressingly ineffective. In hardly any other disease can so little be done to ease the patient's suffering, let alone bring about any clinical improvement."

In the present study of 7576 cases of acute leukemia the highest remission rate is sixty-one per cent. Table I gives the results of management of acute leukemia with nine of the most frequently employed chemicals. Since the types of acute leukemia are so difficult to differentiate, especially in children, no breakdown into lymphocytic, myelocytic, monocytic, and other types is made in this survey of the medical literature since 1949.

TABLE I

CHEMICAL MANAGEMENT OF ACUTE LEUKEMIA

Chemicals	No. of References	No. of Cases	No. of Remissions	No. of Refs. Not Giving Remissions	Remission Rates
FAA	167	2992	1307	15	47%
ACTH/Cortisone	140	1865	942	10	53%
6-MP	76	1654	853	5	57%
N-mustards	61	251	77	3	40%
Antibiotics	22	162	58	4	52%
Radiophosphorus	16	145	31	2	22%
TEM	29	128	53	4	45%
Urethan	22	107	31	3	61%
Colchicines	18	35	13	2	37%
Miscellaneous	59	237	98	7	—

* Furman University, Greenville, South Carolina.

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A serious limitation to a critical evaluation of the management of acute leukemia by chemotherapy is the number of investigations which fail to record the number of patients treated and/or the number responding. Table I gives this shortcoming of the medical literature. The remission rates in the last column are calculated from reports which give both the number of patients treated and those responding.

The absence of objective standards is another general limitation in the evaluation of the several chemotherapeutic agents. The data have been collected from scores of medical centers in many countries, and the reports vary from those supported with detailed clinical and laboratory findings to subjective reactions of the patients and general impressions of attending physicians. Comments on the toxicity and other undesirable reactions of the therapy are given in the discussions of the individual agents.

Folic Acid Antagonists (FAA). The folic acid antagonists, chiefly aminopterin and amethopterin, have been the chemicals of first choice in the management of acute leukemia. Fifteen of the 167 published reports do not give data on the number of patients treated and/or the number responding, but even so FAA account for 40% of the 7576 cases in this review of the literature. Abbasy, Dacie, Klingberg, Meyer, and Murphy all describe serious toxic reactions of the drugs, ending fatally in several cases. Cintra and Soto reported FAA hastened the downhill course of the disease, while Dacie and Ruggeri noted heavy hemorrahages during treatments. Wetherley reported liver damage in a child, and Sansone described neurological complications in two patients.

ACTH/Cortisone. These steroid hormones have been the method of choice of a number of investigators, and the 942 remissions of Table I are impressive. Several investigators, however, have reported that the action of the hormones was contraindicated (Björkman, Darte, Fessas, Joseph, Peel, Rosenthal and Thompson). Kingsley-Pillers and Taylor reported hemorrhages following steroid therapy, and Saric described large rectovaginal and rectoperineal perforations during cortisone administration. Saulnier noted less resistance to T. B. after the use of ACTH, and Oehme recorded polycythemia following ACTH therapy. Nabarro warned of adrenal cortex suppression with prednisone.

6-Mercaptopurine (6-MP). 6-MP shows the highest remission rate of the three most frequently used chemotherapeutic agents in the control of acute leukemia. There have also been fewer complaints of toxicity and other undesirable side effects in the use of this chemical. Gold noted the association of hyperuricemia with 6-MP therapy.

Nitrogen Mustards. N-mustards have one of the lowest remission rates of the remaining chemicals of Table I. Twenty-five of the 61 published reports credit little or no response to this agent which has been so successful in chronic leukemias. The new derivatives, R48, CB1348 and nitromin, have fared little better than HN2 and HN3 in the management of acute leukemia. Dudik noted leukopenic reactions after nitromin therapy.

Antibiotics, Urethan and Colchicines. These three agents make the best showing of the remaining antileukemic compounds of Table I. Barnard warned of conjestive failure, and Rottino of brain mycosis during antibiotic therapy. Six of the 22 reports on the use of urethan gave negative results, and Cifarelli stated the drug hastened the course of the disease in one of 8 patients. One-half of the reports on the administration of colchicines to patients with acute leukemia were unfavorable.

Triethylene Melamine (TEM) and Radiophosphorus (P^{32}). Eight of the 29 reports on TEM therapy were negative, and only four investigators noted complete remissions with this chemical. One-third of the reports on the use of P^{32} in acute leukemia described little or no benefit, and Karnaukhov found the action was contraindicated in acute and subacute cases.

Miscellaneous Agents. Several dozen new chemicals are grouped under this head in the search for agents to control acute leukemia. One-third showed unfavorable reactions, and half a dozen proved to be harmful (Greenspan, Heilmeyer, Paolino, Rausch, Smith and Weisberger). None was tested sufficiently to give data of statistical value.

Acknowledgments

The original literature was made available by the National Library of Medicine, and the libraries of Furman University and the Greenville General Hospital.

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STUDIES OF THE GENUS THYMUS
PART VI

Comparison of the Diagnostic Microscopical Characteristics of Thymus hirsutus Bieb. and Thymus heterotrichus Griseb.

By Ikram Hassan * and M. S. Dunn **

THE microscopical studies were continued by the authors of the various species of Thymus mentioned by Bailey (2). This paper includes our studies of Thymus hirsutus Bieb. and Thymus heterotrichus Griseb.

Five samples of Thymus hirsutus were obtained from (a) Philadelphia Academy of Natural Sciences, (b) Harvard University Herbarium, (c) United States National Herbarium, (d) Botanische Staatassammlung, Munchen, Nymphenburg, (e) Bailey Hortorium; and two samples of Thymus heterotrichus were examined from (f) Botanical Garden, Kew and (g) Botanische Garten und Museum, Berlin.

The material used in these studies, although obtained from the herbarium sheets collected or identified by recognized plant taxonomists, was still checked for authenticity by comparison with the descriptions given by Bailey (2), and Lacaita (3).

Method of Study

The studies of the two species described in this paper were carried out essentially in the same manner as explained in our earlier paper (1).

A palisade number count, and a count of leaf stomata per small central square unit of the Howard micrometer ruling were also made in a number of cases.

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** Professor of Biology and Director of the Biology Department, Philadelphia College of Pharmacy and Science, Philadelphia, Pa.

Summary

On the basis of detailed microscopical descriptions, not published in this paper, of Thymus hirsutus Bieb. and Thymus heterotrichus Griseb., the following summary is given of our findings:

I. The comparison of the palisade numbers of Thymus hirsutus based on an average of 12 counts and of Thymus heterotrichus on an average of 8 counts did not seem to be of value in the separation of these species. The palisade number of Thymus hirsutus averaged 11.0 while that of Thymus heterotrichus was 10.6.

II. The average number of stomata of the lower epidermis of the floral leaf per central square of the Howard micrometer ruling based on 4 counts in case of Thymus hirsutus was 17.0 while that of Thymus heterotrichus based on an average of 8 counts was 9.9.

III. A comparison of the principal histological differences of the two species is given below:

A. Floral Leaf

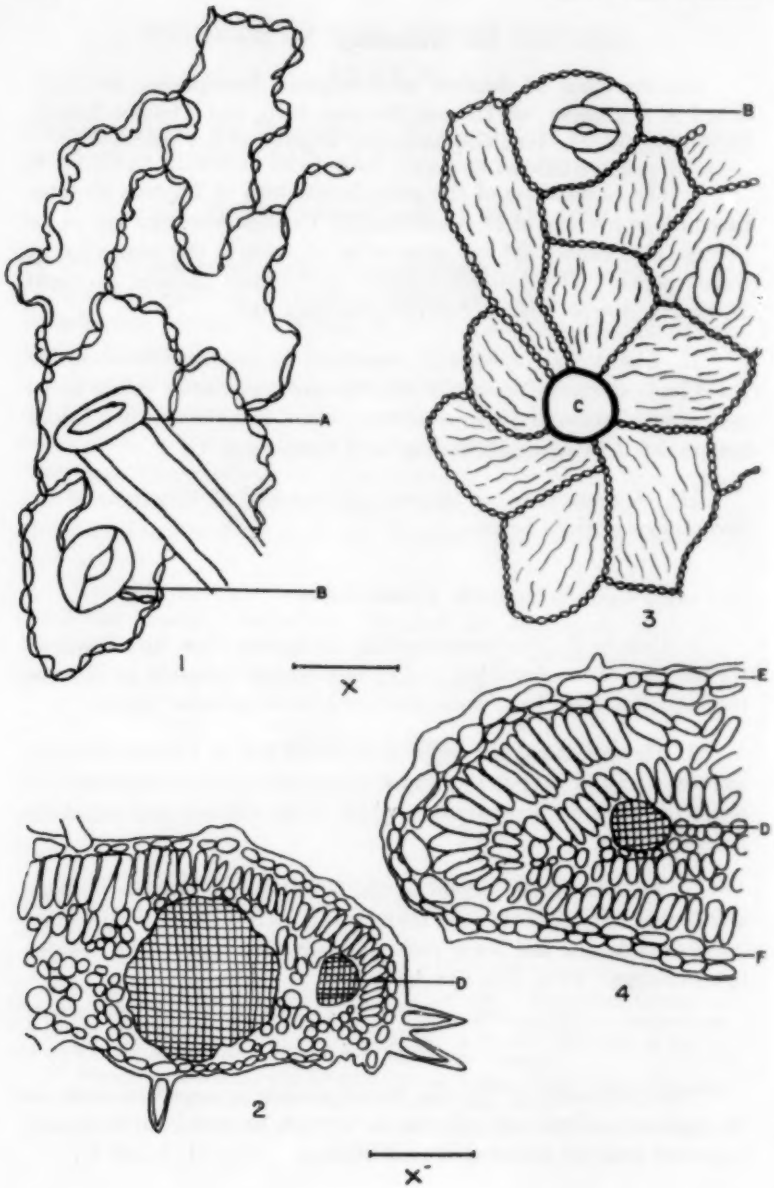
1. One to 7 celled nonglandular trichomes were found around the margins of the floral leaf in Thymus hirsutus whereas in Thymus heterotrichus these hairs were restricted to the petiolar regions.

2. The epidermal cell walls of the floral leaf in Thymus hirsutus were thicker and irregularly beaded as compared to the epidermal cell walls of Thymus heterotrichus which were thinner and regularly beaded. (Fig. I, 1 and 3.)

3. The transverse section of the floral leaf of Thymus hirsutus was devoid of hypodermis and lower palisade layer whereas upper and lower hypodermal and lower palisade layers were present in Thymus heterotrichus. (Fig. I, 2 and 4.)

B. Stem

The trichomes in Thymus hirsutus were arranged in rows on the epidermis of the stem whereas in Thymus heterotrichus they were scattered over the entire epidermal surface. (Fig. II, 1 and 4.)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C. Calyx

1. In Thymus hirsutus the outer epidermis of the tubular region of the calyx in the interrib region had cells without any papilla-like projections, whereas in Thymus heterotrichus these cells were raised into striated papillae due to the continuation of the general epidermal cuticular striations. (Fig. II, 2 and 5.)

2. In Thymus hirsutus, the cells under the outer epidermis in the divided region, when seen in surface view, were not rounded but resembled spongy parenchyma, (Fig. II, 3), but in Thymus heterotrichus the corresponding cells were round and resembled palisade cells in end view.

3. All the five sepals in both Thymus hirsutus and Thymus heterotrichus had 1-4 celled marginal nonglandular hairs.

D. Corolla

In Thymus hirsutus, long 1-celled trichomes on the inner surface of the corolla tube with shrunken walls, but without peg-like projections were present. These hairs were entirely absent in Thymus heterotrichus.

E. Foliage Leaf

The histological structures of the foliage leaf of both Thymus hirsutus and Thymus heterotrichus did not present marked histological variations when compared with the floral leaf of the same species.

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FIGURE I

Thymus hirsutus

1. The upper epidermis of the floral leaf.
2. Transverse section of the floral leaf.

Thymus heterotrichus

3. Upper epidermis of the floral leaf.
4. Transverse section of the floral leaf.

A. Nonglandular hair partly shown. B. Stoma. C. Base of the glandular hair. D. Veins cut transversely. E. Epidermis. F. Hypodermis.

Camera lucida drawings. Scale X = 34 microns for drawings 1 and 3. Scale X′ = 100 microns. Drawings 2 and 4 semidiagrammatic.

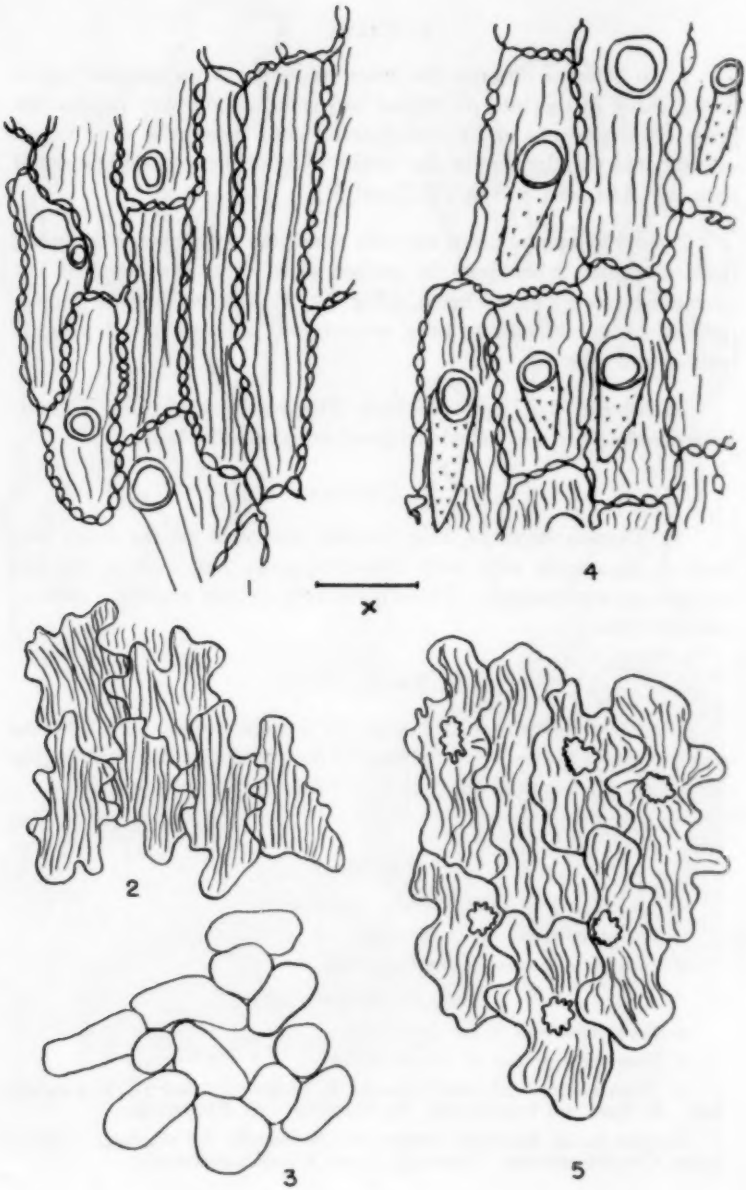
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FIGURE II

THYMUS HIRSUTUS

1. Portion of epidermis of the stem showing trichomes in rows.

2. Outer epidermis of the calyx tube in the interrib region, showing cuticular striations.

3. Parenchymatous tissue below the outer epidermis of calyx with intercellular spaces (surface view).

THYMUS HETEROTRICHUS

4. Portion of epidermis of the stem showing trichomes scattered over the whole surface.

5. Outer epidermis of the calyx tube in the interrib region, showing striated papillae.

Camera lucida drawings. Scale X = 34 microns for all drawings.

STUDIES OF THE GENUS THYMUS
PART VII

Comparison of the Diagnostic Microscopical Characteristics of Thymus pectinatus Fisch. and Thymus Zygis Linn.

By Ikram Hassan * and M. S. Dunn **

THE histological studies of Thymus pectinatus Fisch. mentioned by Bailey (1), and Thymus Zygis Linn. selected because of its economic importance, were made by the authors and are reported in this paper.

The authentic sample of Thymus pectinatus Fisch. was obtained from Museum National D' Histoire Naturelle Laboratoire De'-Phanerogamie, Paris, France. Four true samples of Thymus Zygis Linn. were examined from (a) Martindale Collection of the Philadelphia College of Pharmacy and Science, (b) Philadelphia Academy of Natural Sciences, (c) Botanical Garden of the University of Montreal, and (d) New York Botanical Garden.

The material used in these studies was obtained from herbarium sheet specimens collected or identified by recognized plant taxonomists. The authenticity of this material was checked by comparison with the description given by Bailey (1), Bailey and Bailey (2), and Linné (3).

Method of Study

The studies of Thymus pectinatus Fisch. and Thymus Zygis Linn. were carried out in the same manner as described by Hassan and Dunn (4).

A palisade number count, and a count of the leaf stomata per small central square unit of the Howard micrometer ruling were also made whenever feasible.

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** Professor of Biology and Director of the Biology Department, Philadelphia College of Pharmacy and Science, Philadelphia, Pa.

Summary

The following is the summary of our findings, based on more detailed microscopical data not published in this paper.

I. The comparison of the palisade numbers of Thymus pectinatus based on an average of 4 counts and of Thymus Zygis on an average of 12 counts did not seem to be of value in the separation of these species. The palisade number of Thymus pectinatus averaged 14.0 while that of Thymus Zygis was 15.2.

II. Because of the narrowness of the floral leaf of Thymus pectinatus, the determination of the average number of stomata of the lower epidermis of the floral leaf per small central square of the Howard micrometer was found practical only in Thymus Zygis. The average value for Thymus Zygis based on 12 counts was 9.2.

III. A comparison of the principal histological differences of the two species is given below:

A. Floral Leaf

1. The upper epidermis in both Thymus species under discussion was composed of cells with slightly wavy, beaded walls, with unstriated cuticle (one specimen of Thymus Zygis, however, showed cuticular striations). The surface nonglandular trichomes although present in Thymus pectinatus were only present in certain specimens of Thymus Zygis. (Fig. I, 1 and Fig. II, 1.)

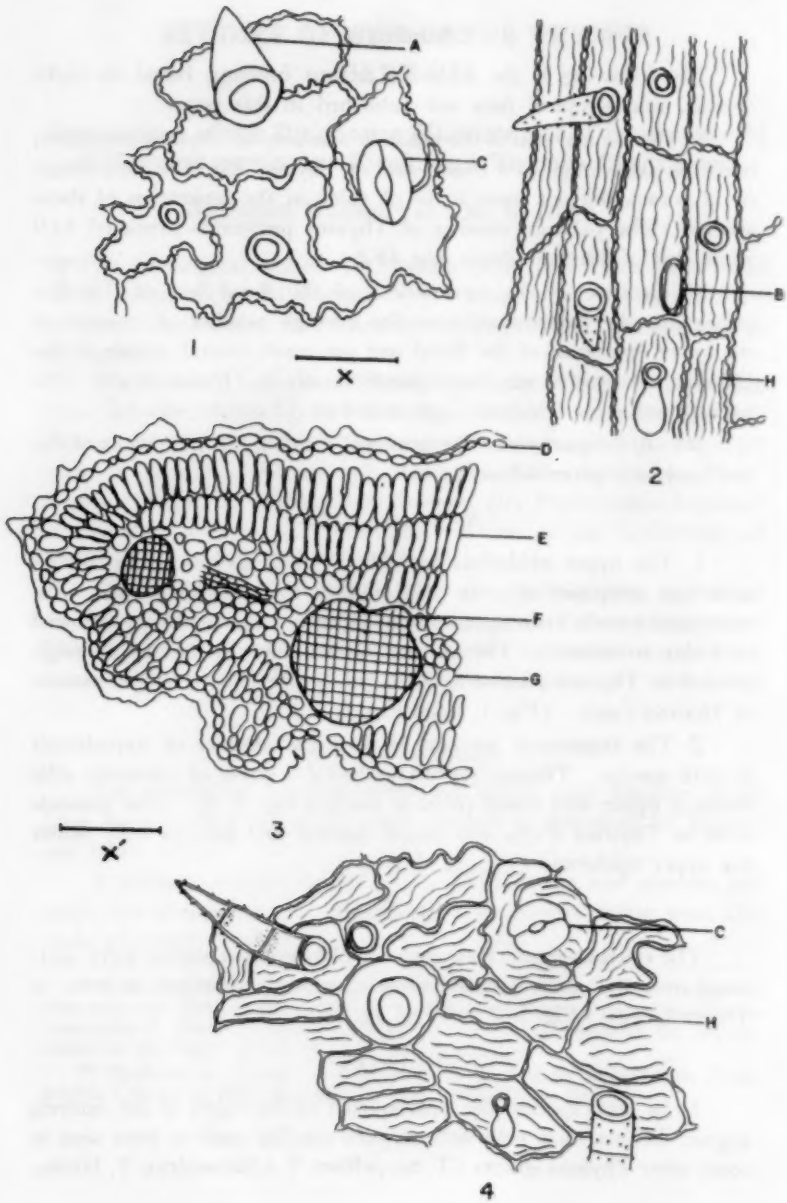
2. The transverse sections showed the absence of hypodermis in both species. Thymus pectinatus had 2-3 layers of columnar cells forming upper and lower palisade zones (Fig. I, 3). The palisade zone in Thymus Zygis was single layered and present only under the upper epidermis (Fig. II, 3).

B. Stem

The trichomes and their scars in Thymus pectinatus were scattered over the entire surface while they were arranged in rows in Thymus Zygis (Fig. I, 2 and Fig. II, 2).

C. Calyx

1. In both species, the tubular part of the calyx in the interrib region, did not show cells with striated papillae such as were seen in some other Thymus species (T. Serpyllum, T. Chamaedrys, T. Herba-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barona, T. striatus, and T. heterotrichus) already discussed in previous papers.

2. In Thymus pectinatus, the cells under the outer epidermis in the divided region when seen in surface view were not round, but resembled irregular spongy parenchyma, whereas in Thymus Zygis, the corresponding cells were round and had the appearance of palisade cells in end view (Fig. II, 6).

3. All sepals, broader as well as narrower, in Thymus pectinatus had 1-4 celled nonglandular hairs on their margins, while in Thymus Zygis the broader sepals had only papilla-like nonglandular hairs and the narrower sepals had 1-4 celled nonglandular hairs (Fig. II, 5A, 5B).

D. Corolla

The 1-celled, long, nonglandular trichomes with shrunken walls on the inner surface of the corolla tube were entirely absent in both Thymus pectinatus and Thymus Zygis, although this hair type was found in certain other species (T. capitatus, T. striatus, T. carnosus, T. villosus, and T. hirsutus).

E. Foliage Leaf

The histological structure of the foliage leaves in both Thymus pectinatus and T. Zygis did not present significant differences from the corresponding floral leaves.

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FIGURE I

Thymus pectinatus

1. Upper epidermis of the floral leaf.
2. Epidermis of the stem showing beaded walls (only partly shown).
3. Transverse section of the floral leaf.
4. Outer epidermis of the calyx in the interrib region.

A. Nonglandular hair. B. Trichome scar. C. Stoma. D. Epidermis. E. Palisade cells. F. Vein cut transversely. G. Spongy tissue. H. Cuticular striation.

Camera lucida drawings. Scale X (for drawings 1, 2 and 4) = 34 microns. Scale X′ (for drawing 3) = 100 microns. Drawing 3 semidiagrammatic.

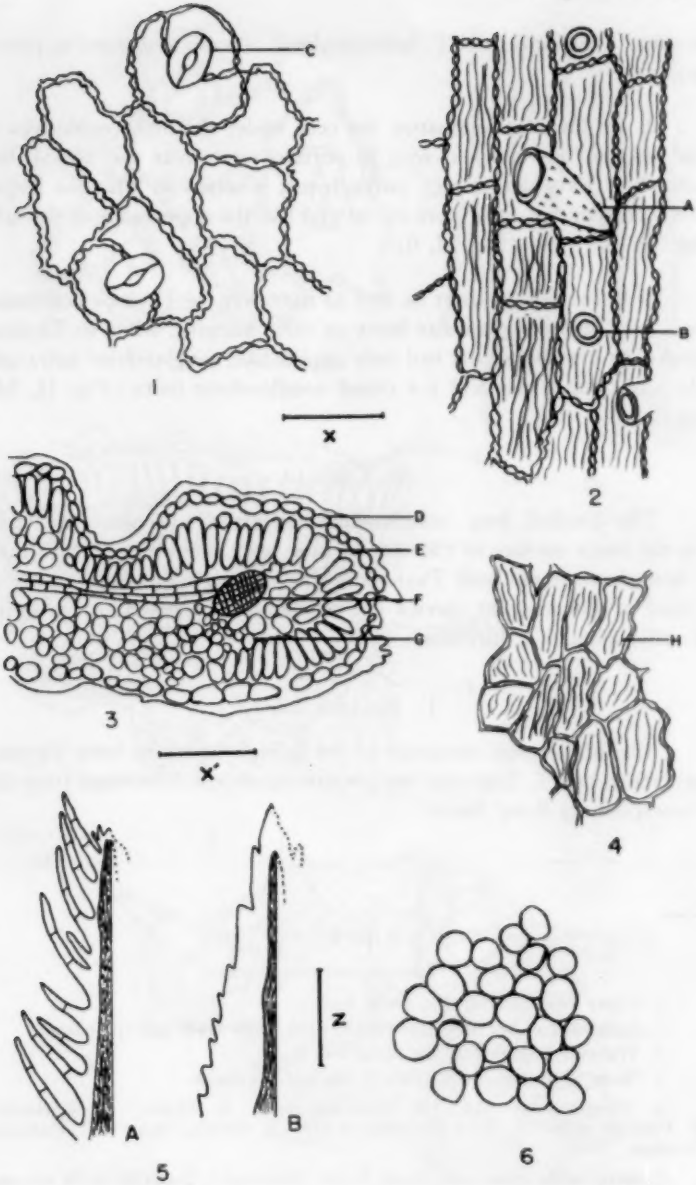
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FIGURE II

THYMUS ZYGIS

1. Upper epidermis of the floral leaf. (Cuticular striations not shown.)

2. Epidermis of the stem (partly shown) showing trichomes and trichome scars.

3. Transverse section of the floral leaf.

4. Outer epidermis of the calyx in the interrib region.

5A. Portion of narrower sepal.

5B. Portion of broader sepal.

6. Palisade-like cells in surface view (calyx region).

A. Nonglandular hair. B. Trichome scar. C. Stoma. D. Epidermis. E. Palisade cells. F. Vein cut transversely. G. Spongy tissue. H. Cuticular striation.

Camera lucida drawings. Scale X (for drawings 1, 2, 4 and 6) = 34 microns. Scale X′ (for drawing 3) = 100 microns. Scale Z (for drawings 5A and 5B) = 300 microns. Drawings 3 and 5 semidiagrammatic.

SELECTED ABSTRACTS

Studies on the Stability of Menadione Sodium Bisulfite Injection. Yeh, S., and Wiese, G. A. *Drug Standards 26:22* (1958). In solution, menadione sodium bisulfite may be converted to the relatively inactive isomer, 2-methyl-1,4-naphthohydroquinone-3-sulfonate. Or, it may develop a yellow color and precipitate in the form of 2-methyl-1,4-naphthohydroquinone. The authors studied various factors which affect the stability of an aqueous solution of menadione sodium bisulfite.

The effect of pH upon a solution of this compound was studied by dissolving menadione sodium bisulfite in a concentration of 4 mg./ml. in distilled water and in various buffer systems. In sealed ampuls stored at 95° C., the solutions developed a yellow color and a crystalline precipitate of 2-methyl-1,4-naphthohydroquinone within about 15 minutes at a pH of 3 or above, but not for about 2 hours at a pH below 3 or in distilled water. Yellow color and precipitate formation was also delayed by increasing the sodium bisulfite content from 0.05 to 0.25 per cent and by the inclusion of 0.85 per cent sodium chloride. Heat and light were also found to accelerate the production of a yellow color and a precipitate.

Sealing the solution under inert gases was found to increase the rate at which the relatively inert isomer, 2-methyl-1,4-naphthohydroquinone-3-sulfonate, was formed.

As a result of these studies the authors proposed the following formula for a stable solution of menadione sodium bisulfite:

Menadione sodium bisulfite, hydrous	0.478	Gm.
Sodium bisulfite	0.2	Gm.
Sodium chloride	0.7	Gm.
Distilled water, to make	100.0	ml.

This solution was filtered and sealed under normal atmosphere in 1 ml. ampuls. The ampuls were then divided into groups and stored at 60, 50, and 40° C. and also at room temperature in direct sunlight. The latter developed a yellow color within two months. In contrast, the solution in ampuls stored in an oven at 60° C. developed no color nor precipitate for one year. The shelf life of this formula was estimated, on the basis of the accelerated studies at higher temperatures, to be 2½ years at 20° C., 2 years at 25° C. and 1½ years at 30° C.

Inactivation of Pyrogens by Gamma Radiation. Whittet, T. D., and Hutchinson, W. P. *J. Pharm. and Pharmacol. 9:*950 (1957). Ionizing radiations in doses of 2×10^6 rad have been found to kill most microorganisms, including spores. Somewhat higher doses are required to inactivate viruses. Such radiation dosages do not cause destruction of most chemical molecules and do not produce radioactive materials.

Because of the interest in the possible use of radiation methods to sterilize blood plasma, the authors investigated the effect of gamma radiations on pyrogens, since these are possible contaminants of plasma. London unsterilized tap water, shown to be pyrogenic with low potency, and a purified lipopolysaccharide pyrogen obtained from *Salmonella abortus equi* were used as the sources of pyrogenic material. The dose of London tap water given would, before radiation, be expected to produce a rise in temperature in rabbits of about 1.5° C. The purified pyrogen given was about 250 times the dose which, before radiation, could be expected to give a response of 0.6° C. Samples of each of the pyrogenic materials were irradiated with various doses of gamma radiation and then injected into test rabbits.

The radiation of London tap water with doses up to 3.0×10^6 rad had little effect on its pyrogenicity. Doses of 5.0×10^6 rad produced variable results but doses of 10 to 20 $\times 10^6$ rad produced samples which easily passed the B. P. Pyrogen Test. The purified pyrogenic material required doses of 20×10^6 rad to appreciably reduce its pyrogenicity and doses of 25×10^6 rad to reduce the pyrogenicity sufficiently to pass the B. P. test.

Thus, it would appear that gamma radiations will destroy pyrogens. However, the dosages required are considerably higher than those required to destroy microorganisms and may well be of such magnitude that damage to the product would occur.

An Evaluation of a New Bismuth Salt by In Vitro Methods. Bateson, P. R. *J. Pharm. and Pharmacol. 10:*123 (1958). Frequently, agents used in the treatment of peptic ulcer are evaluated primarily on the basis of their ability to neutralize hydrochloric acid. The author pointed out that pepsin inactivation may be a more important criterion for evaluation. It was suggested that an ideal agent should maintain gastric contents at a pH of 2-4 and at the same time inactivate pepsin.

In vitro methods for the evaluation of the ability of a substance to neutralize acid were described and used by the author. One method, originated by Brindle, was based upon the determination of the change in pH of a given volume of artificial gastric juice. Another method, developed by the author (MCP Method), employed artificial gastric juice having the same formula contained in an artificial stomach. Fresh juice was added at the rate of 1.5 ml. per minute. After each 20 minute period, 30 ml. of the mixture was removed and tested for free pepsin. The pH was recorded continuously. Pepsin was determined on the basis of its ability to cause aggregation of casein particles in fresh homogenized milk.

A new bismuth salt, bismuth aluminate [$Bi_2(Al_2O_4)_3\ 10H_2O$], was tested and compared with bismuth carbonate and bismuth subnitrate as well as aluminum hydroxide, aluminum glycinate, magnesium oxide, magnesium carbonate, magnesium trisilicate, calcium carbonate, and sodium bicarbonate.

All three of the bismuth salts were found to inactivate pepsin but bismuth aluminate was superior to the other two salts. Neither bismuth carbonate nor bismuth subnitrate were good antacids but bismuth aluminate effectively neutralized acid and maintained the pH between 2 and 4, the most desirable range. Bismuth aluminate, aluminum glycinate, and aluminum hydroxide gel were found to be the most effective antacid and antipeptic agents tested. However, although there was little difference in antacid activity, bismuth aluminate was more effective than the other two substances as an antipeptic agent. To equal the antipeptic activity of bismuth aluminate, aluminum glycinate required a dose that would cause side effects from the glycine. With aluminum hydroxide gel, the initial antipeptic activity is reduced as the pepsin adsorbed is gradually washed off again by the addition of fresh acid. Therefore, its antipeptic power is gradually diminished as pepsin is reactivated.

The author pointed out that other properties of preparations intended for use in peptic ulcer therapy, such as coating and sedative properties, may have to be evaluated. In addition, clinical testing must be carried out. However, the methods described, in the opinion of the author, provide an improved means for comparing the antacid and antipeptic properties of an agent preliminary to clinical testing. By these methods, bismuth aluminate was found to be superior to other commonly employed agents as an antacid and antipeptic agent in the treatment of peptic ulcer.

BOOK REVIEWS

Quantitative Organic Analysis. James S. Fritz and George S. Hammond. ix + 303 pp. 1957. John Wiley and Sons, Inc., New York 16, N. Y. Price $6.50.

This book is not an elementary text devoted to "cook book" directions for the analysis of various organic compounds. Conversely, the fourteen chapters are concerned mainly with the many problems encountered in the development of new analytical methods. The first part reviews the various factors involved in designing analytical procedures and the many methods utilized such as non-aqueous titrations, oxidative-reductive, manometric methods, elemental analysis, etc. The latter half discusses the physical methods including spectrophotometric and polarographic techniques with an entire chapter devoted to the solution of new analytical problems. Many of the chapters are concluded with very challenging problems which are ideal from the teaching aspect.

A. R. GENNARO

Organic Syntheses. Volume 36. N. J. Leonard, Editor. v + 120 pp. 1956. John Wiley and Sons, Inc., New York 16, N. Y. Price $3.75.

Volume 36 of this annual work is composed in the style similar to the previous volumes. It includes thirty-five rigorously checked syntheses characteristic of the most widely used methods of synthetic organic chemistry. Four of the procedures; diazomethane, 2-furoic acid, α-naphthylisothiocyanate and *o*- and *p*-nitrobenzaldiacetate are improvements or modifications of those found in previous volumes. The index is cumulative from volume 30.

A. R. GENNARO

Organic Syntheses. Volume 37. James Cason, Editor. vii + 109 pp. 1957. John Wiley and Sons, Inc., New York 16, N. Y. Price $4.00.

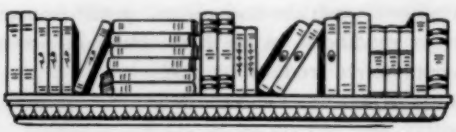
This volume is written in a style similar to the previous, now thumb worn, issues. Included are twenty nine well checked syntheses characteristic of the commonly used procedures in organic chemistry. Several interesting syntheses such as; diaminouracil hydrochloride, 4-hydroxy-1-butanesulfonic acid sultone, various 1,2,3-triazoles and 3-methyloxindole are presented. The index is cumulative for volumes 30 through 37.

A. R. GENNARO

Organic Reactions. Volume IX. Roger Adams, Editor-in-Chief. vii + 468 pp. 1957. John Wiley and Sons, Inc., New York 16, N. Y. Price $12.00.

The ninth volume of this extensive, well known work consists of seven chapters dealing with: Cleavage of Non-enolizable Ketones with Sodium Azide; Gatterman Synthesis of Aldehydes; Bayer-Villiger Oxidation of Aldehydes and Ketones; Alkylation of Esters and Nitriles; Reaction of Halogens with Silver Salts of Carboxylic acids; Synthesis of β-Lactams and Pschorr Synthesis and Related Diazonium Ring Closure Reactions. The chapter dealing with β-lactam formation is especially timely due to Dr. Sheehan's recent synthesis of penicillin. Each chapter has the usual fine bibliography and a subject index is included for the entire book.

A. R. GENNARO



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